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ORIGINAL ARTICLE

Plasma Calcium and Risk of Hypertension: Propensity Score Analysis Using Data From the Korean Genome and Epidemiology Study

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Abstract
Objective: To investigate associations between plasma calcium and future incidence of hypertension in a healthy population.
Methods: We used prospective data from Ansung and Ansan cohorts (n = 10,038) of the Korean Genome and Epidemiology Study. Data from baseline (2001—02) to the fourth study (2007—08) were used. After excluding hypertensive cases at baseline, missing data, and outliers, 5560 participants were analyzed. Propensity scores for having higher plasma calcium ($\geq$2.37 mmol/L) were created for each participant. After propensity score matching (1:1 nearest neighbor matching within caliper), 2153 pairs were left for analysis. Factors that were significantly different between the lower and higher plasma calcium groups before matching either became nonsignificant or the difference decreased in size.
Results: Using multivariable Cox proportional hazard models with robust standard errors accounting for clustering of matched pairs, higher plasma calcium was associated with higher incidence of hypertension (adjusted HR, 1.24; robust 95%CI, 1.07—1.43). Among those with higher plasma calcium, low dietary calcium intake increased the development of hypertension, but the effect was not significant. Sensitivity analysis showed that our results were robust to hidden bias.
Conclusions: Plasma calcium was positively associated with incidence of hypertension. These results expand on cross-sectional associations between hypercalcemia and the metabolic syndrome, and extend the link to future risk of hypertension.

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1. Introduction

Hypertension is a growing public health problem [1] and a strong risk factor for cardiovascular disease worldwide [2,3]. The prevalence of hypertension in Korea was reported to be 28.9% among men and 15.9% among women [4].

There have been some studies reporting associations between plasma calcium and hypertension; moreover, acute hypercalcemia [5,6] and chronic hypercalcemia due to hyperparathyroidism or other causes [7,8] are often accompanied by hypertension, whereas acute hypocalcemia is known to induce hypotension [9,10]. The mechanisms involved in calcium-mediated blood pressure (BP) control are incompletely understood, but peripheral vasoconstriction appears to play a role [6]. Recently, a link between plasma calcium and parathyroid hormone (PTH) with metabolic syndrome was suggested in a cross-sectional study [11]. This link may be translated into an association between hypercalcemia and future risk of hypertension; however, few prospective data on the topic are available, particularly in the general population.

We analyzed data from two well-established, population-based, prospective cohorts of the Korean Genome and Epidemiology Study (KoGES), first established in 2001, to investigate the effects of plasma calcium on incidence of hypertension.

2. Subjects and Methods

2.1. Study population

KoGES is an ongoing series of prospective cohort studies conducted by the Korea Centers for Disease Control and Prevention. The participants comprise Korean adults aged 40−69 years; the total number of participants is expected to reach 300,000 by 2012. The community-based cohorts in Ansung (a rural area) and in Ansan (an urban community) were the first cohorts of KoGES, established in 2001. The baseline survey was conducted from May 2001 to February 2003 in 10,038 participants, including 4763 men and 5275 women; follow-up surveys have been performed every other year since then. Among the 10,038 participants at baseline, subjects who were either hypertensive (including those on antihypertensive medication) ($n = 3142$) or failed to return to follow-up ($n = 1147$) were excluded from this analysis. An additional 189 patients who were outliers or had missing values with respect to the plasma calcium level were excluded. In this study, data from the baseline study to the third (2007−08) follow-up survey were used, which encompassed 6 years of follow-up. This study was approved by the institutional review board or the Korea Centers for Disease Control and Prevention, and followed the ethical principles for medical research involving human subjects outlined in the Helsinki declaration.

2.2. Blood pressure measurements

Measurements for blood pressure and other clinical and laboratory tests, as well as various definitions, are described in the Supplementary Methods online.

2.3. Statistical analysis

First, plasma calcium levels were classified into quartiles, namely Q1 thru Q4: Q1 for <2.28 (mean, 2.17) mmol/L, Q2 for 2.28≤2.37 (mean, 2.33) mmol/L, Q3 for 2.37≤2.44 (mean, 2.41) mmol/L, and Q4 for ≥2.44 mmol/L (mean, 2.50) mmol/L. We then computed incidence ratio of hypertension within different quartiles of plasma calcium level using person-time of follow-up from baseline examination to diagnosis of hypertension at a subsequent examination, or day of the last follow-up examination, whichever came first.

To reduce impact of selection bias and potential confounding we performed adjustments for significant differences in characteristics of participants by propensity score matching [12,13]. Detailed methods for propensity score matching and other statistical analyses are described in the Supplementary Methods online.

3. Results

3.1. Baseline characteristics and incidence of hypertension according to plasma calcium

A total of 5560 participants (male/female, 2750/2810) were included in the analysis. Baseline characteristics of the study participants are presented in Supplementary Table 1. Participants with higher baseline plasma calcium level had positive correlations with older age, smoking, rural area of residence, systolic BP, presence of microalbuminuria, and serum total cholesterol and triacylglyceride (TG). There were inverse correlations between plasma calcium and BMI, serum glucose, and high-density lipoprotein cholesterol (HDL-C) levels. Plasma calcium increased with higher dietary calcium intake, but the trend in the association was not significant.

During the 6 years of follow-up, we identified 1017 incident cases of hypertension. The incidence rates of hypertension per 1000 person-years for quartiles Q1 thru Q4 of plasma calcium levels were 6.1, 6.2, 7.6, and 8.7, respectively (p-trend < 0.001; not shown on tables).

3.2. Propensity score estimation and matching

After performing propensity score matching in the entire population, overall distribution of propensity scores was compared between those with higher and lower plasma calcium levels (Figure 1). Common support region needed for matching seemed sufficient for 1:1 matching, and a total of 2153 matched pairs of

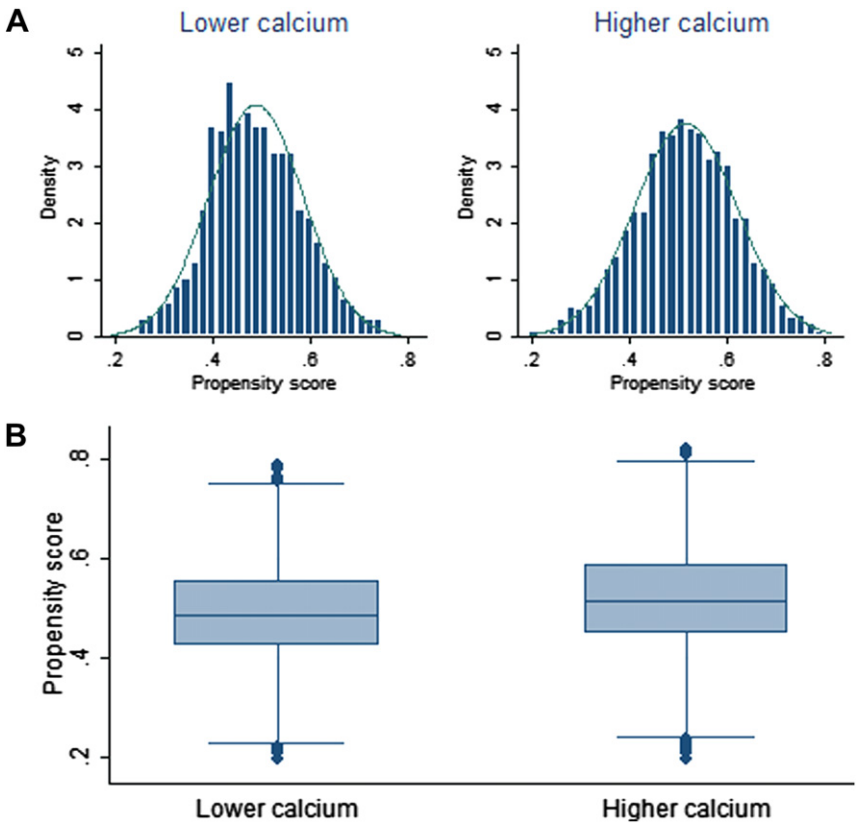

Figure 1. Distribution of propensity scores among participants with lower and higher plasma calcium levels. Lower calcium, plasma calcium <2.37 mmol/L; higher calcium, plasma calcium ≥2.37 mmol/L.

participants were created. After matching, factors that were significantly different between the lower and higher plasma calcium groups became either nonsignificant or the difference decreased in size (Table 1).

3.3. Multivariable analysis for incidence of hypertension with higher level of plasma calcium

Multivariable analysis using Cox proportional hazards models based on factors that were significant at baseline is represented in Table 2. Before propensity score matching, plasma calcium ≥2.37 versus <2.37 mmol/L was associated with significantly higher risk for developing hypertension (adjusted hazard ratio [HR], 1.29; 95% confidence interval [95%CI], 1.14−1.47). This association remained significant after the propensity score matching (adjusted HR, 1.24; robust 95%CI, 1.07−1.43).

3.4. Cumulative incidence of hypertension with higher and lower levels of plasma calcium

With higher level of plasma calcium (≥2.37 mmol/L), cumulative incidence of hypertension was significantly higher as shown by Kaplan-Meier curves both before and after propensity score matching (Figure 2). Although the significance was rather attenuated after matching, it was still highly significant (log-rank $p = 0.008$).

3.5. Interaction between plasma calcium and dietary calcium intake

Among participants with higher level of plasma calcium, development of hypertension during follow-up was higher among those with the lowest dietary calcium intake (Q1 *vs.* Q2−4, 105/493 [21.3%] *vs.* 284/1546 [18.4%]), although the difference was not statistically significant (Figure 3). Logistic regression, including the interaction term between dietary calcium intake and plasma calcium, was also not statistically significant (data not shown).

3.6. Sensitivity of study results to hidden bias

Using the Mantel-Haenszel bounds method, sensitivity analysis showed that the effects of higher plasma calcium could not be explained away, even at large values of Γ (Supplementary Table 2). This shows that the study result was highly robust to hidden bias.

4. Discussion

In this population-based prospective cohort study various risk factors for hypertension and their

Table 1. Baseline characteristics of participants before and after propensity score matching[a]

Characteristics	Before matching (n = 5560)			After matching (n = 4306)		
	Lower calcium[b]	Higher calcium[c]	p	Lower calcium[b]	Higher calcium[c]	p
Age, years	50.5 ± 8.7	51.5 ± 8.5	<0.001	51.1 ± 0.2	51.0 ± 0.2	0.724
Smoking, n (%)			0.027			0.514
Never	1619 (56.5)	1603 (59.4)		1300 (60.4)	1279 (59.4)	
Ever	1245 (43.5)	1093 (40.5)		853 (39.6)	874 (40.6)	
Area, n (%)			0.254			0.170
Ansung (rural)	1403 (49.0)	1362 (50.5)		1092 (50.7)	1047 (48.6)	
Ansan (urban)	1461 (51.0)	1334 (49.5)		1061 (49.3)	1106 (51.4)	
Plasma calcium, mmol/L	2.26 ± 0.0	2.45 ± 0.0	<0.001	2.27 ± 0.0	2.45 ± 0.0	<0.001
Systolic BP, mmHg	113.9 ± 0.2	114.9 ± 0.2	<0.001	114.5 ± 0.2	114.6 ± 0.2	0.675
Serum creatinine, μmol/L	87.0 ± 11.3	88.1 ± 5.7	<0.001	87.0 ± 11.3	87.7 ± 5.0	0.006
Microalbuminuria, n (%)	102 (3.6)	228 (8.5)	<0.001	100 (4.6)	103 (4.8)	0.829
Serum glucose, mmol/L	4.72 ± 0.02	4.61 ± 0.03	0.002	4.59 ± 0.03	4.64 ± 0.03	0.212
BMI, kg/m^2	24.6 ± 0.1	24.4 ± 0.1	0.011	24.5 ± 0.1	24.5 ± 0.1	0.810
Total cholesterol, mmol/L	4.93 ± 0.02	4.88 ± 0.02	0.031	4.87 ± 0.02	4.89 ± 0.02	0.554
HDL-C, mmol/L	1.18 ± 0.0	1.13 ± 0.0	<0.001	1.17 ± 0.01	1.14 ± 0.01	<0.001
Triacylglyceride, mmol/L	3.68 ± 0.04	4.35 ± 0.05	<0.001	3.82 ± 0.05	4.25 ± 0.06	<0.001
GTP, U/L	29.4 ± 0.9	33.8 ± 1.2	0.003	30.3 ± 1.1	30.7 ± 1.0	0.813

[a]*Factors that were significant in Supplementary Table 1 are shown;* [b]*Plasma calcium <2.37 mmol/L;* [c]*Plasma calcium ≥2.37 mmol/L.*
Mean ± SD unless otherwise stated.
BMI, body mass index; BP, blood pressure; GTP, γ-glutamyl transferase; HDL-C, high-density lipoprotein cholesterol.

associations with the incidence of hypertension were analyzed, and positive association of plasma calcium with incidence of hypertension was shown.

Recently, elevated level of plasma calcium has been reported to be associated with parameters of metabolic syndrome and insulin resistance [11,14]. Although the underlying mechanisms are not fully understood, PTH seems to play some role, possibly by proliferative effect on vascular smooth muscle cells contributing to vessel wall thickening [15] PTH also indirectly increases vascular smooth muscle intracellular calcium by activating vitamin D, which results in contraction and increased peripheral vascular resistance [16,17]. In our study, serum PTH was not measured; therefore, its role in development of hypertension could not be analyzed. However, plasma calcium was significantly associated with future risk of hypertension, which extends the previously reported cross-sectional correlation [18−20]. Hypercalcemia has also been shown to induce hypertension in dogs, where intravenous infusion of $CaCl_2$ caused increased mean arterial blood pressure, total peripheral resistance, and renal vascular resistance [21].

Associations between dietary calcium intake and blood pressure were reported in some studies [5,22,23], but not in others [6,7,24]. Overall, there seems a small degree of BP reduction with increasing dietary intake of calcium [7]. Since the BP-lowering effect of calcium supplementation appears small, studies with substantial heterogeneity in terms of participant characteristics, measurement of BP outcomes, and dose and method of calcium supplementation might result in different conclusions. In our study, the amount of calcium intake (mean, 485 mg/d) was lower compared with previous studies, where even higher intake of calcium (mean, 825 mg/d) did not reduce either the blood pressure or the risk of developing hypertension [24]. Although not significant in this study, the interaction between the effects of dietary calcium intake and plasma calcium on development of hypertension did seem rather conspicuous. The amount of calcium intake in our study was assessed by semi-quantitative food frequency questionnaires [25]. Further studies with higher intake of calcium and more detailed survey on calcium intake could reveal more significant findings.

Table 2. Multivariable adjusted hazard ratios for hypertension with higher plasma calcium[a] before and after propensity score matching

	No. cases/total	Person-years	Unadjusted		Adjusted[b]	
			HR (95%CI)	p	HR (95%CI)	p
Before matching	1016/5560	25,810	1.42 (1.25−1.61)	<0.001	1.29 (1.14−1.47)	<0.001
After matching[c]	776/4306	20,016	1.24 (1.07−1.42)	0.003	1.24 (1.07−1.43)	0.004

[a]*Reference, lower plasma calcium (<2.37 mmol/L);* [b]*Adjusted for sex, age, alcohol, smoking status, cohort, baseline SBP, serum creatinine, BMI, fasting plasma glucose, GTP, total cholesterol, HDL-C, and TG;* [c]*Robust standard errors used, accounting for clustering of matched pairs.*

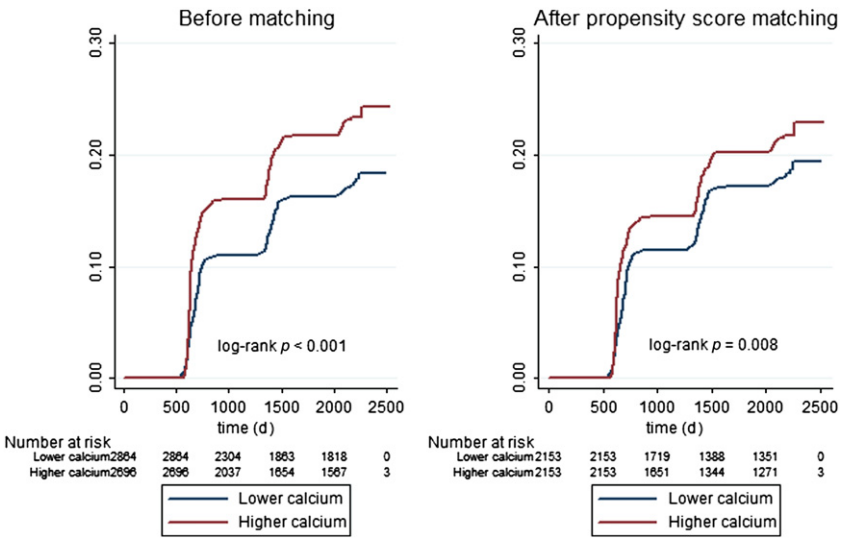

Figure 2. Kaplan-Meier estimates of cumulative incidence of hypertension.

In our study, baseline plasma calcium was positively associated with higher systolic BP, serum creatinine, and tendency towards dyslipidemic profile (higher TG and lower HDL-C), which is consistent with previous reports [11,26]. Cardiovascular risk factors tend to occur in clusters, and plasma calcium was already associated with multiple cardiovascular risk factors at baseline. To balance the differences between higher and lower plasma calcium groups, we performed propensity score matching analysis. Although the differences in serum creatinine, HDL-C, and TG between the groups remained significant, they decreased after matching. Also, there were only a few cases of clinically significant levels of azotemia or dyslipidemia that could have caused hypertension in the higher-plasma calcium group. By balancing most of the covariates between the groups, we were able to minimize selection bias and assess the impact of having higher plasma calcium on development of hypertension with minimal attribution of confounding variables. We also adjusted for serum creatinine and other potential confounding variables in the final multivariable analysis so as further to minimize selection bias.

There were several limitations in this study. First, the follow-up time of 6 years was relatively short, which could be insufficient for development of a chronic disease such as hypertension. Second, the serum level of PTH was not measured. PTH plays a crucial role in

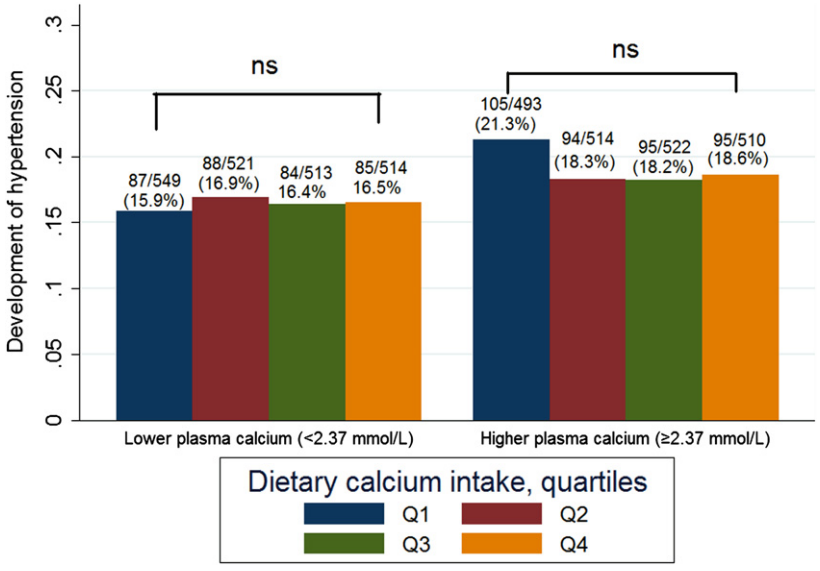

Figure 3. Development of hypertension among participants with higher and lower levels of plasma calcium according to quartiles of dietary calcium intake. Dietary calcium intake quartiles: Q1, <301; Q2, 302−432; Q3, 433−604; Q4, ≥605 mg/d.

calcium metabolism, and PTH may have had a confounder effect. Third, there was no repeat calcium measurement during follow-up. Initial plasma calcium levels could merely reflect a snapshot at a particular time, and long-term effects of such a measurement are not certain. Fourth, clinical application of the findings of this paper is limited, since only plasma calcium values within normal limits were analyzed. Finally, some of the variables that were significantly different between higher and lower plasma calcium levels before propensity score matching remained significant even after matching. Although these variables were adjusted in the multivariable analysis, they could have caused some confounding effect.

In conclusion, we showed that a higher level of plasma calcium was associated with increased incidence of hypertension. This study also indicated that plasma calcium levels tend to correlate with other cardiometabolic risk factors.

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Supplementary Material

Supplementary data related to this article can be found online at doi:10.1016/j.phrp.2011.07.004.

References

1. Elliott WJ. Systemic hypertension. Curr Probl Cardiol 2007;32: 201−59.
2. Kubo M, Hata J, Doi Y, et al. Secular trends in the incidence of and risk factors for ischemic stroke and its subtypes in Japanese population. Circulation 2008;118:2672−8.
3. Sjol A, Thomsen KK, Schroll M. Secular trends in blood pressure levels in Denmark 1964−1991. Int J Epidemiol 1998;27: 614−22.
4. Jee SH, Appel LJ, Suh I, et al. Prevalence of cardiovascular risk factors in South Korean adults:results from the Korea Medical Insurance Corporation (KMIC) Study. Ann Epidemiol 1998;8: 14−21.
5. Weidmann P, Massry SG, Coburn JW, et al. Blood pressure effects of acute hypercalcemia. Studies in patients with chronic renal failure. Ann Intern Med 1972;76:741−5.
6. Marone C, Beretta-Piccoli C, Weidmann P. Acute hypercalcemic hypertension in man: role of hemodynamics, catecholamines, and renin. Kidney Int 1981;20:92−6.
7. Earll JM, Kurtzman NA, Moser RH. Hypercalcemia and hypertension. Ann Intern Med 1966;64:378−81.
8. Kisch ES, Dluhy RG, Williams GH. Regulation of renin release by calcium and ammonium ions in normal man. J Clin Endocrinol Metab 1976;43:1343−50.
9. Shackney S, Hasson J. Precipitous fall in serum calcium, hypotension, and acute renal failure after intravenous phosphate therapy for hypercalcemia. Report of two cases. Ann Intern Med 1967;66:906−16.
10. Llach F, Weidmann P, Reinhart R, et al. Effect of acute and long-standing hypocalcemia on blood pressure and plasma renin activity in man. J Clin Endocrinol Metab 1974;38:841−7.
11. Ahlstrom T, Hagstrom E, Larsson A, et al. Correlation between plasma calcium, parathyroid hormone and the metabolic syndrome in a community-based cohort of men and women. Clin Endocrinol (Oxf) 2009;71:673−8.
12. Rosenbaum P, Rubin D. The central role of the propensity score in observational studies for causal effects. Biometrika 1983;70: 41−55.
13. D'Agostino Jr RB. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med 1998;17:2265−81.
14. Hagstrom E, Hellman P, Lundgren E, et al. Serum calcium is independently associated with insulin sensitivity measured with euglycaemic-hyperinsulinaemic clamp in a community-based cohort. Diabetologia 2007;50:317−24.
15. Perkovic V, Hewitson TD, Kelynack KJ, et al. Parathyroid hormone has a prosclerotic effect on vascular smooth muscle cells. Kidney Blood Press Res 2003;26:27−33.
16. Zemel MB. Calcium modulation of hypertension and obesity: mechanisms and implications. J Am Coll Nutr 2001;20: 428−435S. discussion 440−2S.
17. Lind L, Hanni A, Lithell H, et al. Vitamin D is related to blood pressure and other cardiovascular risk factors in middle-aged men. Am J Hypertens 1995;8:894−901.
18. Robinson D, Bailey AR, Williams PT. Calcium and blood pressure. Lancet 1982;2:1215−6.
19. Kesteloot H, Geboers J, Van Hoof R. Epidemiological study of the relationship between calcium and blood pressure. Hypertension 1983;5:II52−6.
20. Folsom AR, Smith CL, Prineas RJ, Grimm Jr RH. Serum calcium fractions in essential hypertensive and matched normotensive subjects. Hypertension 1986;8:11−5.
21. Eiam-Ong S, Punsin P, Sitprija V, Chaiyabutr N. Acute hypercalcemia-induced hypertension: the roles of calcium channel and alpha-1 adrenergic receptor. J Med Assoc Thai 2004;87:410−8.
22. van den Hoogen PC, Feskens EJ, Nagelkerke NJ, et al. The relation between blood pressure and mortality due to coronary heart disease among men in different parts of the world. Seven Countries Study Research Group. N Engl J Med 2000;342:1−8.
23. Lind L, Skarfors E, Berglund L, et al. Serum calcium: a new, independent, prospective risk factor for myocardial infarction in middle-aged men followed for 18 years. J Clin Epidemiol 1997; 50:967−73.
24. Margolis KL, Ray RM, Van Horn L, et al. Effect of calcium and vitamin D supplementation on blood pressure: the Women's Health Initiative Randomized Trial. Hypertension 2008;52:847−55.
25. Third Korea National Health and Nutrition Examination Survey (KNHANES III); 2006.
26. Kesteloot H, Joossens JV. Relationship of serum sodium, potassium, calcium, and phosphorus with blood pressure. Belgian Interuniversity Research on Nutrition and Health. Hypertension 1988;12:589−93.